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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,396	12/28/2001	Ryoichi Nagata	2001_1906A	8735

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EXAMINER	
SHEIKH, HUMERA N	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,396	NAGATA, RYOICHI	
	Examiner	Art Unit	
	Humera N Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the request for extension of time (3 months-granted), the Amendment, Applicant's Arguments/Remarks and the Affidavit/Exhibits, all filed 05/11/04 is acknowledged.

Claims 1, 2, 5, 7 and 9-12 are pending. No amendments to the claims have been made. Claims 1, 2, 5, 7 and 9-12 remain rejected.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 5, 7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanagawa (US Pat. No. 6,197,328 B1) *or* Yanagawa (EPO 0 681 833 A2).

Yanagawa ***(US '328)*** teaches a nasally administrable composition, comprising an effective amount of a physiologically active compound, insulin and a fine particulate carrier, calcium carbonate having many pores, whereby the porous calcium carbonate has a mean particle size from 15-300 microns and a particle surface area from 0.1 m^2/g to 0.4 m^2/g and wherein the nasally administered formulation contains insulin dispersed and homogeneously adsorbed onto the calcium carbonate carrier and is highly absorbable into the body via the nasal route (see reference column 1, line 1 – column 8, line 16); examples and abstract.

According to Yanagawa, the nasally administrable composition can nasally administer the physiologically active compound, insulin, with higher bioavailability and with less irritability than preparations so far proposed using the carrier, wherein the carrier adheres to the mucous membrane of the nasal cavity (col. 1, lines 45-51).

Yanagawa teaches that the carrier of his invention is characterized by homogeneous dispersion to the interior of the nasal cavity, adhesion to the mucous membrane of the nasal cavity without inhalation to the lung, and the sustainable adhesion of the carrier on the mucous membrane by its own weight and particle size. Such a carrier is a calcium compound, such as *calcium carbonate,* calcium stearate, calcium chloride or calcium hydroxide, wherein among them, calcium carbonate is preferred and has a mean particle size from 15-300 microns and a particle surface area from 0.1 m^2/g to 0.4 m^2/g. The carrier to be used has many pores on the surface as a result of granulation or re-granulation with carriers with each other (col. 2, line 54 – col. 3, line 10).

Examples of physiologically active compounds include peptides, antidiabetics/symptomatic antidiabetics, etc., wherein peptides, such as insulin are preferred. A preferable mode of the invention is a nasally administrable composition having fine particulate of insulin dispersed and adsorbed homogeneously onto the unique mixed carrier of calcium carbonate and high substituted hydroxypropylcellulose (HPC –H) (col. 3, lines 27-55).

The physiologically active compound, insulin, is contained at a rate from 0.0001% to 30% by total weight of the composition (col. 3, line 56 – col. 4, line 4). This range meets the applicant's claimed range of an insulin content of 0.1-50% by weight.

The composition may further contain conventional excipients such as fillers, stabilizers, binders, lubricants and the like (col. 4, lines 11-20).

The examples demonstrate various preparations of the composition of the invention. Test Example 2 at column 5, demonstrates the teaching of a preparation comprising insulin as the selected physiologically active compound, calcium carbonate as the selected carrier and HPC – H was selected as the absorption accelerator to prepare the composition. These ingredients were admixed to make the composition containing insulin 50 IU/50 mg of calcium carbonate/5mg of HPC – H capsule and the resulting mixture was filled into capsules. The mean particle size of each carrier was from 20 microns to 45 microns. The resultant composition was nasally administered once at a dose of 50 mg. The composition containing 50 IU of insulin attained a high degree of absorption of insulin into the blood through the nasal route compared with the comparative composition in which 100 IU of insulin was contained.

Similarly at column 6, a powdery insulin composition for nasal administration was prepared using ingredients of insulin, calcium carbonate and HPC – H.

With regards to the applicants claimed ranges, the prior art teaches similar or overlapping ranges that read on the ranges as instantly claimed. For instance, Yanagawa teaches a mean particle size of the porous calcium carbonate to be 15 – 300 microns (applicant's range is 20 – 32 microns). Additionally, the insulin content taught by the prior art is from 0.0001% to 30% (applicant's range is 0.1-50%). The particle surface area of calcium carbonate taught by Yanagawa is from 0.1 m^2/g to 0.4 m^2/g (applicant's range is 1.5 m^2/g or greater). The surface area taught is slightly less than applicant's claimed surface area, however, it would have been obvious to one of ordinary skill in this art that suitable ranges or amounts could be determined

through routine or manipulative experimentation to obtain the best possible results, as these are indeed variable parameters.

Regarding the particular shape of the crystals (i.e., trabeculate, needle-shaped or aggregation of parallel intergrowth), one of ordinary skill in this art would determine suitable variations of form, which meet the intended or desired purpose.

There is no significant distinction observed between the instant invention and the prior art, since the prior art clearly teaches a nasally administered formulation of insulin, comprising porous calcium carbonate as its carrier, wherein the calcium carbonate has similar particle size and surface area as claimed and whereby the insulin is dispersed and adsorbed homogeneously onto the calcium carbonate. Hence, the instant invention is rendered unpatentable and obvious over Yanagawa (US '328).

Yanagawa ***(EPO '833 A2)*** teaches a nasally administrable composition containing a physiologically active substance – insulin, homogeneously dispersed in and adsorbed homogeneously onto a unique crystalline metal compound carrier, calcium carbonate, whereby the carrier has a mean particle size of not more than 250 microns, or more preferably 30 microns to 60 microns and whereby the formulation is administered via the nasal cavity in a powder formulation (see reference pages 2-4) and Abstract.

According to Yanagawa, the composition, which is prepared by homogeneously dispersing the physiologically active peptide, insulin, in a unique carrier, can be applied to the mucous membrane of the nasal cavity to thereby allow a clinically effective treatment.

Yanagawa teaches that the technique of homogeneously dispersing a physiologically active peptide, insulin, in a carrier, calcium carbonate, provides an equal or higher bioavailability compared with that obtained by injection or oral administration (page 3, lines 2-5).

The carrier includes a calcium compound, such as calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, etc., wherein calcium carbonate is particularly preferred (page 3, lines 33-53).

Various physiologically active substances may be used, and include antidiabetics/symptomatic antidiabetics. A preferred mode of the invention is a nasally administrable composition comprising a physiologically active substance and a physiologically acceptable powdery or crystalline polyvalence metal carrier whose mean particle size is not more than 250 microns and more preferably 30-60 microns (page 4, lines 20-42). Among the physiologically active peptides, peptide hormones, such as insulin are preferred (pg. 5, lines 37-42).

The physiologically active peptide is contained in the composition at a rate from approximately 0.005% to approximately 30% (pg. 6, lines 28-31). This range meets the applicant's claimed range of 0.1-50% insulin content.

The examples taught by Yanagawa show the use of glucagon in combination with calcium carbonate and the use of insulin with hydroxyapatite. Both examples teach the use of peptide hormones in combination with an accepted carrier (see pages 7, 19 and 25).

Regarding the particular shape of the crystals (i.e., trabeculate, needle-shaped or aggregation of parallel intergrowth), one of ordinary skill in this art would determine suitable

variations of form, which meet the intended or desired purpose. Furthermore, the prior art teaches a crystalline or powdery carrier.

Regarding the instant ranges of particle diameter and surface area for calcium carbonate, Yanagawa teaches similar or overlapping ranges for the particle size and is silent as to the specified surface area. However, it is deemed obvious to one of ordinary skill in this art that suitable ranges or amounts could be determined through routine or manipulative experimentation to obtain the best possible results, as these are considered variable parameters. No criticality is seen in the instant ranges, since the prior art clearly teaches a nasally administered formulation comprising similar ingredients (i.e., insulin, calcium carbonate) for a similarly intended purpose as the applicants and in the same field of endeavor, whereby high bioavailability of insulin is obtained using nasal administration. Hence, the instant invention is rendered obvious and unpatentable over Yanagawa (EPO '833 A2).

Response to Arguments

Applicant's arguments filed 05/11/04 have been fully considered but they are not persuasive.

The Applicant argued, "Serum insulin concentrations in Yanagawa are enormously lower than those conducted by the Applicant, despite twice the insulin dose of Yanagawa (US '328). The formulation based on the instant invention enables a higher maximum insulin concentration when compared with Yanagawa."

These arguments have been fully considered but were not found persuasive because the prior art desires an effective amount of active ingredient and the amount of active ingredient recited in Yanagawa (US '328) at column 4, lines 1-4, is within Applicant's desired ranges.

With regards to the Declaration/Exhibit submitted by Applicant, the Declaration has been carefully considered but was not found to be persuasive. The Declaration does not show any unexpected results over the prior art teachings for the use of calcium carbonate particles as a carrier for insulin. The desired insulin concentrations would be routinely established by one of ordinary skill in the art, through the use of routine or manipulative experimentation with the various calcium carbonates available.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays from 8:00 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

H. N. Sheikh H. N. S.

Patent Examiner

Art Unit 1615

August 26, 2004

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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